REMARKS

Claim status

Claims 1, 2, 4-23, 25-28, 30, 31, 34-40, 42-49 and 52-77 are pending. Claims 5-7, 10, 13-15, 20, 21, 22, 26, 31, 36, 39, 40, 46, 47, 48, 58, 61, 64, 65, 70, 71, 72 and 75 are objected claims. Claims 1, 2, 4, 8, 16-19, 20, 21, 23, 25, 27, 28, 30, 34, 35, 42-45, 46, 47, 49, 52-57, 59, 60, 66-69, 70, 71 73, 74, 76 and 77 are rejected claims. Claims 9, 11, 12, 37, 38, 60, 62 and 63 are not objected or rejected claims. Applicants respectfully request whether such claims have been deemed allowable.

Claims 1, 2, 5, 20, 21, 27, 28, 31, 46, 47, 55, 56, 58, 70 and 71 have been amended. Claims 1, 27 and 55 have been amended to replace "wherein at least one sequence for" has been replaced with "which encode" in step b). Claims 2, 5, 28, 31, 56 and 58 have been recast as independent claims which include all the elements of the base claim and any intervening claims. Claims 20, 21, 46, 47, 70 and 71 have been amended to begin with an article and recast as independent claims which include all the elements of the base claim and any intervening claims. No new matter has been added.

Formal Drawings

Applicants direct the Examiner's attention to the formal drawings being filed concurrently in response to the Notice of Draftsperson's Patent Drawing Review (PTO-948).

Objection to Claims 20, 21, 46, 47, 70 and 71

Claims 20, 21, 46, 47, 70 and 71 are objected to "because of the following informalities: Each claim should begin with a capital letter, preferably an article" (Office Action, page 2).

Claims 20, 21, 46, 47, 70 and 71 have been amended to begin with an article, thereby obviating the objection.

Claims 5-7, 10, 13-15, 22, 26, 31, 36, 39, 40, 48, 58, 61, 64, 65, 72 and 75 "are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims" (Office Action, page 3).

Claim 10 and 14 depend from Claim 9 (and Claim 15 depends from Claim 14), which has not been rejected. Claim 22 and 26 depend from Claim 11, which has not been rejected. Claims 36 and 40 depend from Claim 35, which has not been rejected. Claim 39 depends from Claim 38, which has not been rejected. Claim 48 depends from Claim 37, which has not been rejected. Claims 61 and 65 depend from Claim 60, which has not been rejected. Claim 64 depends from Claim 63, which has not been rejected. Claims 72 and 75 depend from Claim 62, which has not been rejected. Therefore, Applicants respectfully request clarification as this objection.

Nevertheless, Claims 5, 31 and 58, which do depend from rejected claims, have been recast as independent claims which include all the elements of the base claim and any intervening claims, thereby obviating the objection.

Rejection of Claims 1, 2, 4, 8, 27, 28, 30, 34, 55-57 and 59 under 35 U.S.C. §112, first paragraph

Claims 1, 2, 4, 8, 27, 28, 30, 34, 55-57 and 59 are rejected under 35 U.S.C. §112, first paragraph.

Written Description

The Examiner notes that the "prior rejection of claims 1-52 have been modified and applies to amended and new claims 1, 2, 4, 8, 27, 28, 30, 34, 55-57 and 59" (Office Action, page 3). The Examiner states that "the specification only teaches antimicrobial peptides and is silent with regard to what kind of therapeutic peptides the claims are encompassing" (Office Action, page 4). The Examiner further states that "[i]t is not sufficient to define peptide solely by its principal biological property . . . because disclosure of no more than that, as in the instant case, is simply a wish to know the identity of any peptide with that biological property" and that "claiming all peptides that achieve a result without defining what means will do so is not in compliance with the description requirement" (Office Action, page 4). The Examiner concludes that "the specification fails to provide an adequate written description of the claimed invention in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time application was filed, had possession of the claimed invention" (Office Action, pages 4-5).

Applicants respectfully disagree. Claims 1, 27 and 55 have been amended to clearly recite a recombinant vector comprising retroviral vector DNA or at least a portion of the retroviral

vector DNA comprising elements necessary for infection and direction of expression in target cells; and one or more coding sequences which encode a recombinant vector comprising a naturally occurring therapeutic antimicrobial peptide or a biologically active derivative thereof, wherein the antimicrobial peptide or derivative thereof is selected from the group consisting of: melittin, premelittin, prepromelittin, cecropin, prececropin, preprocecropin, magainin, a part thereof, an analogue thereof, a homologue thereof and a combination thereof. These claims do not include a heterologous DNA fragment such as marker peptides, therapeutic peptides, cell cycle regulatory peptides, tumor suppressor peptides, antiproliferation peptides and cytokines. Therefore, particularly as amended, Claims 1, 27, 55 and claims dependent thereon should not be included in the present rejection.

To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention (*Vas-Cath, Inc. v. Mahurkar*, 19 U.S.P.Q.2d 1111,1116 (Fed. Cir. 1991)). There is a strong presumption that an adequate written description of the claimed invention is present in the specification as filed (*In re Wertheim*, 191 U.S.P.Q. 90, 96 CCPA 1976).

In the specification as filed Applicants teach that:

> the heterologous DNA fragment can encode for example a peptide such as a marker peptide (e.g., β-galactosidase, neomycin, alcohol dehydrogenase, puromycin, hypoxanthine phosphoribosyl transferase (HPRT), hygromycin, and secreted alkaline phosphatase), a therapeutic peptide (e.g., herpes simplex virus thymidine kinase, cytosine deaminase, guanine phosphoribosyl transferase (gpt), and cytochrome P450), a cell cycle regulatory peptide (e.g., P.T.O., SDI), a tumor suppressor peptide (e.g., p53), an antiproliferation peptide and a cytokine (e.g., IL-2) (specification, page 13, line 28 - page 14, line 5).

Clearly Applicants have provided a patent specification that describes heterologous DNA that encodes, for example, a therapeutic peptide, in sufficient detail that a person of skill in the art would reasonably conclude that the Applicants had possession of the claimed invention.

Enablement

The Examiner notes that the "prior rejection of claims 1-52 have been modified and applies to amended and new claims 1, 2, 4, 8, 16-19, 23, 25, 27, 28, 30, 34, 42-45, 49, 52-57, 59, 66-69, 73, 74, 76 and 77" (Office Action, page 5). The Examiner states that the specification "does not reasonably provide enablement for making a recombinant vector comprising a combination of recited anti-microbial peptides and *any* and *all* therapeutic peptides" and "does not reasonably provide enablement for treating any and all diseases selected from the group consisting of a genetic defect, cancer, and viral infections" (Office Action, page 5). It is the Examiner's opinion that "the specification fails to provide sufficient support for the full scope of the claims because the specification fails to teach the therapeutic effect for treating viral infection *in vivo*, the specification fails to identify or teach any genetic disease that could be treated by the claimed vector, and the specification fails to deliver the vector *in vivo* to an established tumor directly or via any route of administration" (Office Action, page 7). The Examiner states that the "delivery of ex vivo vector-transfected tumor cells in a nude mouse model does correlate with the tumor therapy in humans" (Office Action, page 7).

Applicants respectfully disagree. As pointed out above, Claims 1, 27 and 55 have been amended to clearly recite a recombinant vector comprising retroviral vector DNA or at least a portion of the retroviral vector DNA comprising elements necessary for infection and direction of expression in target cells; and one or more coding sequences which encode a recombinant vector comprising a naturally occurring therapeutic antimicrobial peptide or a biologically active derivative thereof, wherein the antimicrobial peptide or derivative thereof is selected from the group consisting of: melittin, premelittin, prepromelittin, cecropin, prececropin, preprocecropin, magainin, a part thereof, an analogue thereof, a homologue thereof and a combination thereof. These claims do not include a heterologous DNA fragment such as marker peptides, therapeutic peptides, cell cycle regulatory peptides, tumor suppressor peptides, antiproliferation peptides and cytokines. Therefore, particularly as amended, Claims 1, 27, 55 and claims dependent thereon should not be included in the present rejection.

The first paragraph of § 112 requires nothing more than objective enablement (*In re Marzocchi & Horton* 169 USPQ 367, 369 (CCPA 1971)). In *Marzocchi* the court stated that:

> a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be taken as in compliance with the enabling requirement of the first paragraph of § 112 *unless* there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. Assuming that sufficient reason for such doubt does exist, a rejection for failure to teach how to make and/or use will be proper on that basis; such a rejection can be overcome by suitable proofs indicating that the teaching contained in the specification is truly enabling. Id.

The court further stated that:

> it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Id. at 370.

In the specification as filed, Applicants describe numerous examples of therapeutic peptides (specification, page 13, line 3 - page 14, line 5) and those of skill in the art are aware of many more such peptides. In addition, Applicants have demonstrated that the anti-cancer activity of melittin, cecropins and magainins is known (*e.g.,* specification, page 3, line 21 - page 4, line 18). Particularly, cecropin, prepromelittin and premelittin have been demonstrated by the Applicants as having anti-tumour effects *in vivo* (specification, page 25, lines 6- 26). Antiviral activity was specifically demonstrated by the Applicants for melittin, prepromelittin, premelittin, cecropin and preprocecropin *in vitro* (specification, page 25, line 27 - page 26, line 28).

The Examiner has not provided acceptable evidence or reasoning which casts doubt on Applicant's *in vivo* data. The Examiner states that the "delivery of ex vivo vector-transfected tumor cells in a nude mouse model does [sic] correlate with the tumor therapy in humans" (Office Action, page 7).

Applicants are assuming that the Examiner meant to say that "delivery of ex vivo vector-transfected tumor cells in a nude mouse model does ***NOT*** correlate with the tumor therapy in humans", however, Applicants respectfully request clarification on this point. If Applicants'

assumption is correct, the Examiner appears to be requiring Applicants to provide human data for enablement of the claimed invention. However, this is ***not*** a requirement for patentability (*In re Brana*, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995)). To support the claimed invention, Applicants have provided an *in vivo* animal model which correlates with the claimed methods. That is, one of skill in the art would accept Applicants' *in vivo* model as reasonably correlating to the claimed compositions and methods. A rigorous or an invariable exact correlation is ***not*** required (*Cross v. Iizuka*, 224 U.S.P.Q. 739, 747 (Fed. Cir. 1995); see also MPEP 2164.02).

Applicants have provided an enabling disclosure for the full scope of the claimed invention.

Rejection of Claims 1, 21, 35, 47, 60 and 71 under 35 U.S.C. §112, second paragraph

Claims 1, 21, 35, 47, 60 and 71 are rejected under 35 U.S.C. §112, second paragraph as being "vague and indefinite" because "claims 21, 47, and 71 recite 'RNA of a vector according to' a previous claim drawn to a recombinant DNA vector" (Office Action, page 8).

Claims 21, 47 and 71 have been amended to indicate that the RNA is produced by the recombinant vector of the claims from which they depend, thereby obviating the rejection.

Rejection of Claims 20, 21, 46, 47, 70 and 71 under 35 U.S.C.§102(e)

Claims 20, 21, 46, 47, 70 and 71 are rejected under 35 U.S.C. §102(e) "as being anticipated by *Gilboa* (US 5,658,775)" (Office Action, page 8). The Examiner states that Gilboa "teaches a retroviral vector construct comprising a DNA sequence of interest (claim 1), wherein the DNA sequence will be transcribed into RNA under control of a promoter in the transfected host cells, wherein the RNA is a mRNA molecule (claim 12)" (Office Action, page 9). The Examiner states that "amending claims 20, 21, 46, 47, 70, and 71 to recite the particulars of the recombinant vector in the base claims 1, 9, 35, and 60, respectively, could obviate this rejection" (Office Action, page 9).

Claims 20, 21, 46, 47, 70 and 71 have been amended to recite the particulars of the recombinant vector in the base claims, thereby obviating the rejection.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned at (978) 341-0036.

Respectfully submitted,

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MARKED UP VERSION OF AMENDMENTS

Claim Amendments Under 37 C.F.R. § 1.121(c)(1)(ii)

1. (Four times amended) A recombinant vector comprising, in operable linkage,

   a) retroviral vector DNA or at least a portion of the retroviral vector DNA comprising elements necessary for infection and direction of expression in target cells; and

   b) one or more coding sequences [wherein at least one sequence encodes for] which encode a naturally occurring therapeutic antimicrobial peptide or a biologically active derivative thereof, wherein the antimicrobial peptide or derivative thereof is selected from the group consisting of: melittin, premelittin, prepromelittin, cecropin, prececropin, preprocecropin, magainin, a part thereof, an analogue thereof, a homologue thereof and a combination thereof.

2. (Four times amended) [The] A recombinant vector [according to Claim 1] comprising in operable linkage,

   a) a 5' long terminal repeat region comprising the structure U3-R-U5;

   b) one or more of said coding sequences wherein at least one sequence encodes for a naturally occurring therapeutic antimicrobial peptide or a biologically active derivative thereof, wherein the antimicrobial peptide or derivative thereof is selected from the group consisting of: melittin, premelittin, prepromelittin, cecropin, prececropin, preprocecropin, magainin, a part thereof, an analogue thereof, a homologue thereof and a combination thereof; and

   c) a 3' long terminal repeat region comprising a completely or partially deleted U3 region wherein said deleted U3 region is replaced by a polylinker sequence, followed by the R and U5 region to undergo promoter conversion.

5. (Amended) [The] A recombinant vector [of Claim 4] comprising in operable linkage,

   a) a 5' long terminal repeat region comprising the structure U3-R-U5;

b) one or more coding sequences wherein at least one sequence encodes for at least one naturally occurring therapeutic antimicrobial peptide or a biologically active derivative thereof, wherein the antimicrobial peptide or derivative thereof is selected from the group consisting of: melittin, premelittin, prepromelittin, cecropin, prececropin, preprocecropin, magainin, a part thereof, an analogue thereof, a homologue thereof and a combination thereof; and

c) a 3' long terminal repeat region comprising a completely or partially deleted U3 region wherein said deleted U3 region is replaced by a polylinker sequence which comprises at least one unique restriction site and at least one insertion of a heterologous DNA fragment which [wherein said heterologous DNA fragment] regulates the expression of at least one of the coding sequences of said [retroviral] vector, and comprises at least one or more elements selected from the group consisting of: regulatory elements and promoters.

20. (Amended) A mRNA of a retroviral provirus [according to Claim 12] produced by infection of target cells with a recombinant retroviral particle from a recombinant retroviral vector system comprising:

a) a recombinant vector comprising, in operable linkage,

i) retroviral vector DNA or at least a portion of the retroviral vector DNA comprising elements necessary for infection and direction of expression in target cells; and

ii) one or more coding sequences wherein at least one sequence encodes for a naturally occurring therapeutic antimicrobial peptide or a biologically active derivative thereof, wherein the antimicrobial peptide or derivative thereof is selected from the group consisting of: melittin, premelittin, prepromelittin, cecropin, prececropin, preprocecropin, magainin, a part thereof, an analogue thereof, a homologue thereof and a combination thereof; and

b) a packaging cell line harboring at least one retroviral construct coding for proteins required for said retroviral vector to be packaged.

21. (Amended) A RNA [of] produced by a vector [according to Claim 1] wherein said vector comprises, in operable linkage,

a) retroviral vector DNA or at least a portion of the retroviral vector DNA comprising elements necessary for infection and direction of expression in target cells; and

b) one or more coding sequences wherein at least one sequence encodes for a naturally occurring therapeutic antimicrobial peptide or a biologically active derivative thereof, wherein the antimicrobial peptide or derivative thereof is selected from the group consisting of: melittin, premelittin, prepromelittin, cecropin, prececropin, preprocecropin, magainin, a part thereof, an analogue thereof, a homologue thereof and a combination thereof.

27. (Twice amended) A recombinant vector comprising, in operable linkage,

a) retroviral vector DNA or at least a portion of the retroviral vector DNA comprising elements necessary for infection and direction of expression in target cells; and

b) one or more coding sequences [wherein at least one sequence encodes for] which encode a naturally occurring therapeutic antimicrobial peptide or a biologically active derivative thereof, wherein the antimicrobial peptide or derivative thereof is selected from the group consisting of: melittin, premelittin, prepromelittin, a part thereof, an analogue thereof, a homologue thereof, and a combination thereof.

28. (Twice amended) [The] A recombinant vector [according to Claim 27] comprising in operable linkage,

a) a 5' long terminal repeat region comprising the structure U3-R-U5;

b) one or more of said coding sequences wherein at least one sequence encodes for a naturally occurring therapeutic antimicrobial peptide or a biologically active derivative thereof, wherein the antimicrobial peptide or derivative thereof is selected from the group consisting of: melittin, premelittin, prepromelittin, a part thereof, an analogue thereof, a homologue thereof, and a combination thereof; and

c) a 3' long terminal repeat region comprising a completely or partially deleted U3 region wherein said deleted U3 region is replaced by a polylinker sequence, followed by the R and U5 region to undergo promoter conversion.

31. (Amended) [The] A recombinant vector [of Claim 30] comprising in operable linkage,

a) a 5' long terminal repeat region comprising the structure U3-R-U5;

b) one or more of said coding sequences wherein at least one sequence encodes for a naturally occurring therapeutic antimicrobial peptide or a biologically active derivative thereof, wherein the antimicrobial peptide or derivative thereof is selected from the group consisting of: melittin, premelittin, prepromelittin, a part thereof, an analogue thereof, a homologue thereof, and a combination thereof; and

c) a 3' long terminal repeat region comprising a completely or partially deleted U3 region wherein said deleted U3 region is replaced by a polylinker sequence which comprises at least one unique restriction site and at least one insertion of a heterologous DNA fragment which [wherein said heterologous DNA fragment] regulates the expression of at least one of the coding sequences of said [retroviral] vector, and comprises at least one or more elements selected from the group consisting of: regulatory elements and promoters.

46. (Amended) A mRNA of a retroviral provirus [according to Claim 38] produced by infection of target cells with a recombinant retroviral particle from a recombinant retroviral vector system comprising:

a) a recombinant vector comprising, in operable linkage

i) a retroviral vector DNA or at least a portion of the retroviral vector DNA comprising elements necessary for infection and direction of expression in target cells; and

ii) one or more coding sequences wherein at least one sequence encodes for at least one naturally occurring therapeutic antimicrobial peptide or a biologically active derivative thereof wherein the antimicrobial peptide or derivative thereof is selected from the group consisting of: melittin,

premelittin, prepromelittin, a part thereof, an analogue thereof, a homologue thereof; and a combination thereof; and

b) a packaging cell line harboring at least one retroviral construct coding for proteins required for said retroviral vector to be packaged.

47. (Amended) A RNA [of] produced by a vector [according to Claim 35] recombinant retroviral vector system comprising:

a) a recombinant vector comprising, in operable linkage,

i) retroviral vector DNA or at least a portion of the retroviral vector DNA comprising elements necessary for infection and direction of expression in target cells; and

ii) one or more coding sequences wherein at least one sequence encodes for at least one naturally occurring therapeutic antimicrobial peptide or a biologically active derivative thereof wherein the antimicrobial peptide or derivative thereof is selected from the group consisting of: melittin, premelittin, prepromelittin, a part thereof, an analogue thereof, a homologue thereof, and a combination thereof; and

b) a packaging cell line harboring at least one retroviral construct coding for proteins required for said retroviral vector to be packaged.

55. (Amended) A recombinant vector comprising, in operable linkage,

c) retroviral vector DNA or at least a portion of the retroviral vector DNA comprising elements necessary for infection and direction of expression in target cells; and

d) one or more coding sequences [wherein at least one sequence encodes for] which encode a naturally occurring therapeutic antimicrobial peptide or a biologically active derivative thereof, wherein the antimicrobial peptide or derivative thereof is selected from the group consisting of: cecropin, prececropin, preprocecropin, SB-37, Shiva-1, a part thereof, an analogue thereof, a homologue thereof, and a combination thereof.

56. (Amended) [The] A recombinant vector [according to Claim 55] comprising in operable linkage,

a) a 5' long terminal repeat region comprising the structure U3-R-U5;

b) one or more of said coding sequences wherein at least one sequence encodes for a naturally occurring therapeutic antimicrobial peptide or a biologically active derivative thereof, wherein the antimicrobial peptide or derivative thereof is selected from the group consisting of: cecropin, prececropin, preprocecropin, a part thereof, an analogue thereof, a homologue thereof, and a combination thereof; and

c) a 3' long terminal repeat region comprising a completely or partially deleted U3 region wherein said deleted U3 region is replaced by a polylinker sequence, followed by the R and U5 region to undergo promoter conversion.

58. (Amended) [The] A recombinant vector [of Claim 57] comprising in operable linkage,

a) a 5' long terminal repeat region comprising the structure U3-R-U5;

b) one or more coding sequences wherein at least one sequence encodes for a naturally occurring therapeutic antimicrobial peptide or a biologically active derivative thereof, wherein the antimicrobial peptide or derivative thereof is selected from the group consisting of: cecropin, prececropin, preprocecropin, a part thereof, an analogue thereof, a homologue thereof and a combination thereof; and

c) a 3' long terminal repeat region comprising a completely or partially deleted U3 region wherein said deleted U3 region is replaced by a polylinker sequence which comprises at least one unique restriction site and at least one insertion of a heterologous DNA fragment which [wherein said heterologous DNA fragment] regulates the expression of at least one of the coding sequences of said [retroviral] vector, and comprises at least one or more elements selected from the group consisting of: regulatory elements and promoters.

70. (Amended) A mRNA of a retroviral provirus [according to Claim 63] produced by infection of target cells with a recombinant retroviral particle from a recombinant retroviral vector system comprising:

a) a recombinant vector comprising, in operable linkage,

i) retroviral vector DNA or at least a portion of the retroviral vector DNA comprising elements necessary for infection and direction of expression in target cells; and

ii) one or more coding sequences wherein at least one sequence encodes for at least one naturally occurring therapeutic antimicrobial peptide or a biologically active derivative thereof wherein the antimicrobial peptide or derivative thereof is selected from the group consisting of: cecropin, prececropin, preprocecropin, a part thereof, an analogue thereof, a homologue thereof, and a combination thereof; and

b) a packaging cell line harboring at least one retroviral construct coding for proteins required for said retroviral vector to be packaged.

71. (Amended) A RNA [of] produced by a vector [according to Claim 60] wherein said vector comprises, in operable linkage,

a) retroviral vector DNA or at least a portion of the retroviral vector DNA comprising elements necessary for infection and direction of expression in target cells; and

b) one or more coding sequences wherein at least one sequence encodes for at least one naturally occurring therapeutic antimicrobial peptide or a biologically active derivative thereof wherein the antimicrobial peptide or derivative thereof is selected from the group consisting of: cecropin, prececropin, preprocecropin, a part thereof, an analogue thereof, a homologue thereof, and a combination thereof.